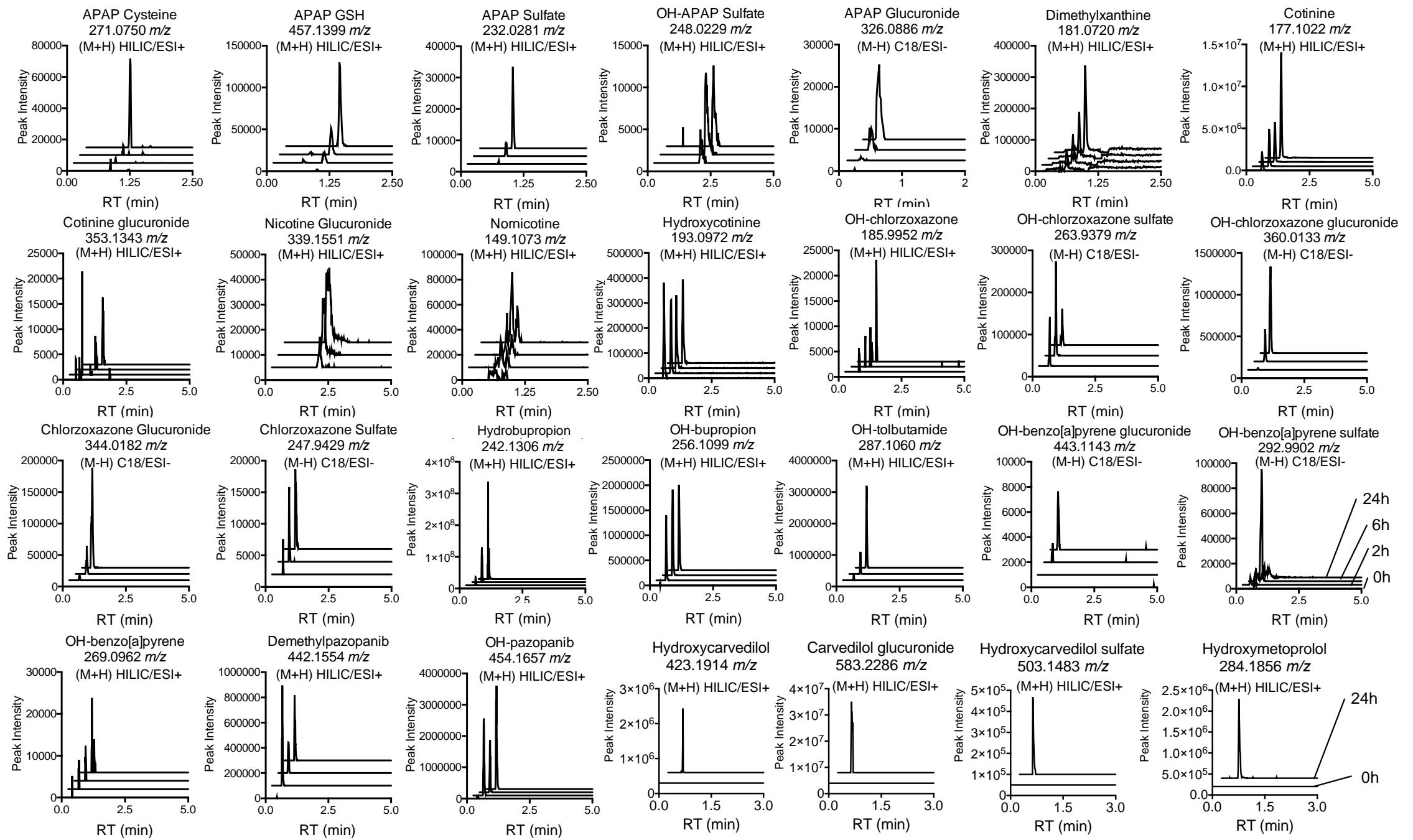


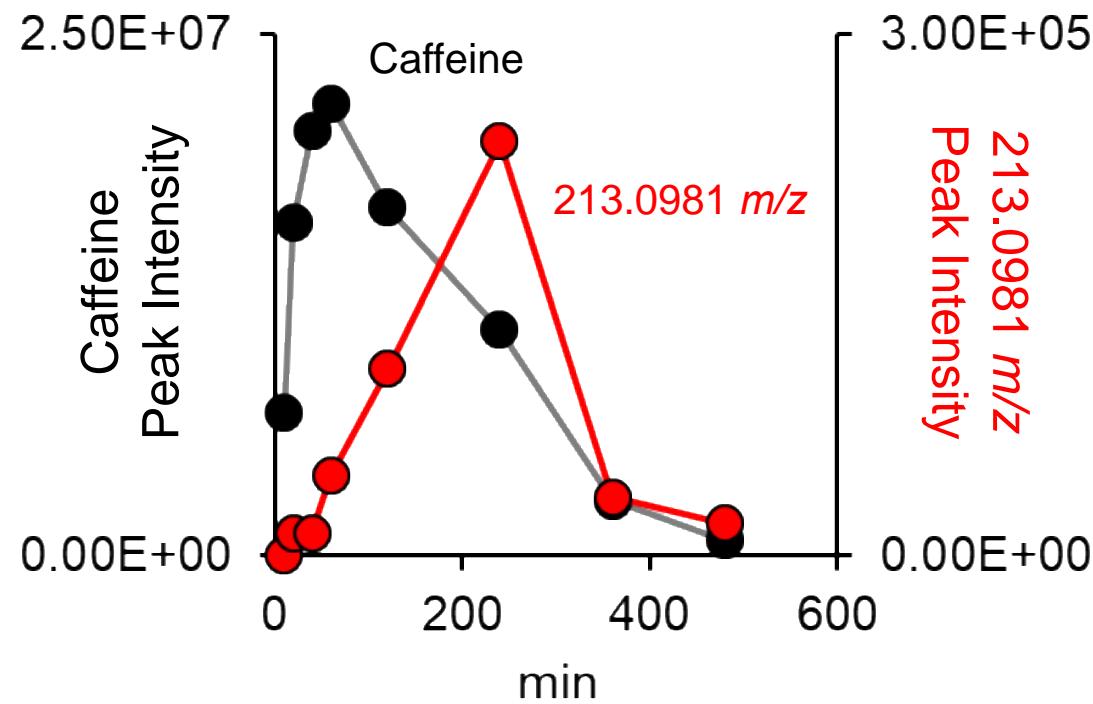
Supplementary information for *Large scale enzyme based xenobiotic identification for exposomics*

- S1: Time-dependent formation of expected metabolites
- S2: Relationship of 213.0981 m/z to caffeine in mice and humans
- S3: Correlations of related metabolites in documented exposures
- S4: Correlations of related metabolites in undocumented exposures
- S5: Time-dependent formation of expected metabolites from mixtures analysis

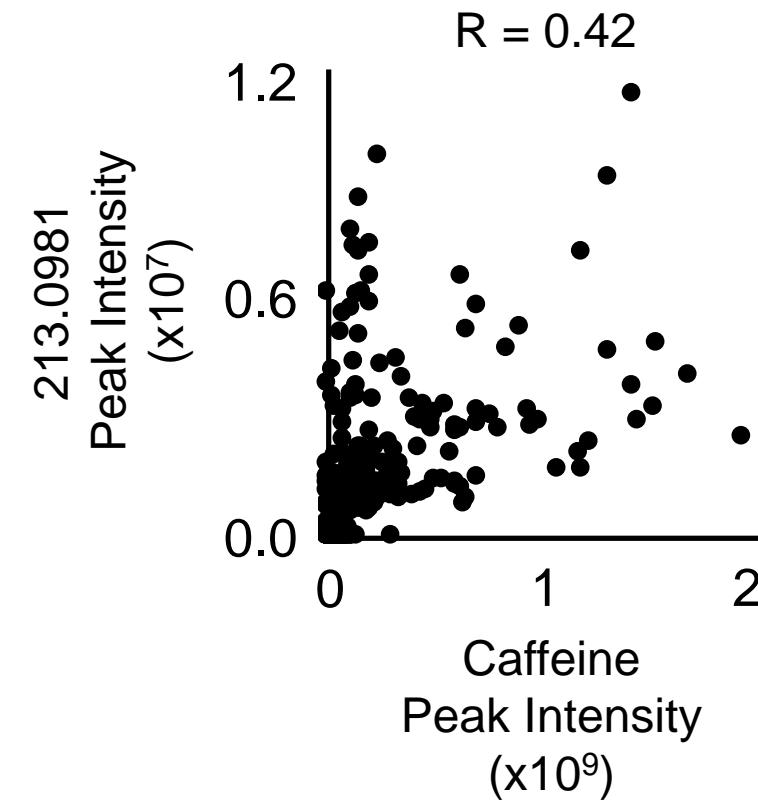


Supplementary Fig. 1. Extracted ion chromatograms for S9 enzymatic reactions showing time-dependent formation (0, 24h) of expected metabolites.

S2a



S2b



Supplementary Fig. 2. Additional data on identification of caffeine related metabolite in experimental samples

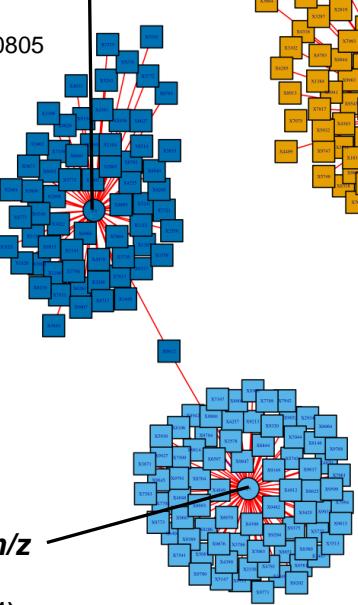
- Pharmacokinetic profile of caffeine and previously uncharacterized caffeine-related metabolite 213.0981 m/z in mouse
- Correlation of caffeine with caffeine-related metabolite 213.0981 m/z in humans (Pearson's R)

S3a**Warfarin 309.1121 m/z**

Associated ions in cluster

Isotopes: 310.1128 (^{13}C)

Source fragments: 163.0390, 147.0805

Hydroxywarfarin (325.1058)Isotopes: 326.1100 (^{13}C)**Bupropion 240.1150 m/z**

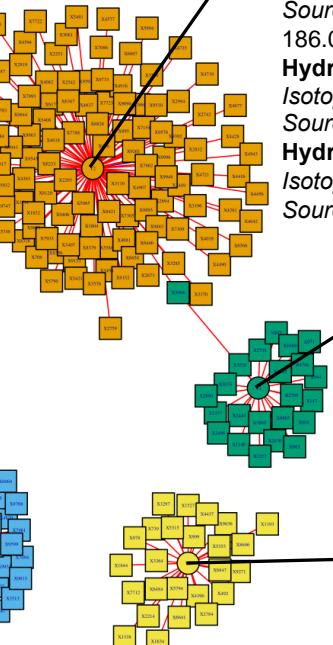
Associated ions in cluster

Isotopes: 241.1176 (^{13}C)

Source fragments: 184.0524, 166.0419,

186.0594 (^{37}Cl)**Hydrobupropion (242.1306)**Isotopes: 243.1340 (^{13}C), 244.1266 (^{37}Cl)Source fragments: 186.0678, 168.0574, 188.0651 (^{37}Cl)**Hydroxybupropion (256.1090)**Isotopes: 257.1130 (^{13}C), 258.1066 (^{37}Cl)

Source fragments: 238.0994, 239.1038, 240.0954

**Acetaminophen 152.0706 m/z**

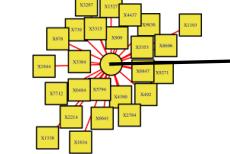
Associated ions in cluster

Isotopes: 153.0740 (^{13}C)**Acetaminophen Glucuronide (328.1027)**

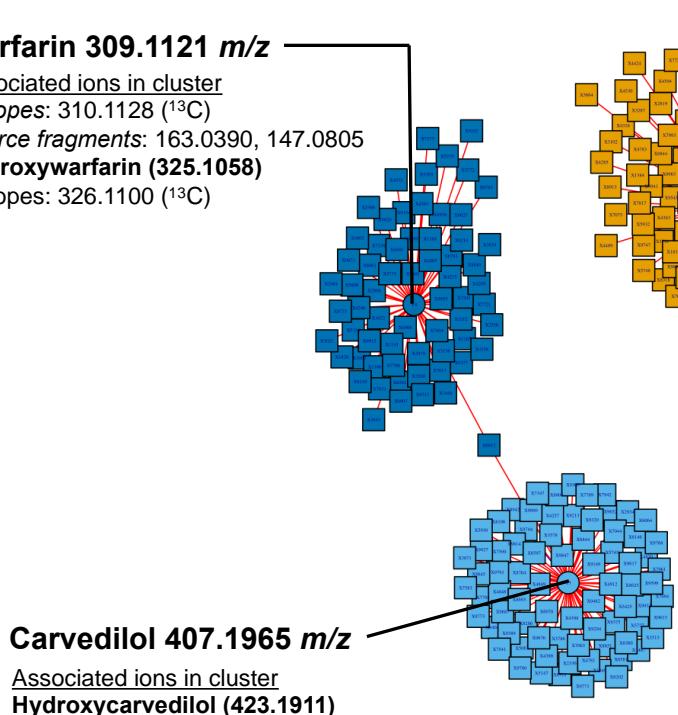
Adducts: 350.0836 (+Na), 366.0585 (+K)

Isotopes: 351.0878 (^{13}C , M+Na)**Metoprolol 268.1907 m/z**

Associated ions in cluster

Isotopes: 269.1939 (^{13}C)**Hydroxymetoprolol (284.1854)**Isotopes: 285.1866 (^{13}C)**Carvedilol 407.1965 m/z**

Associated ions in cluster

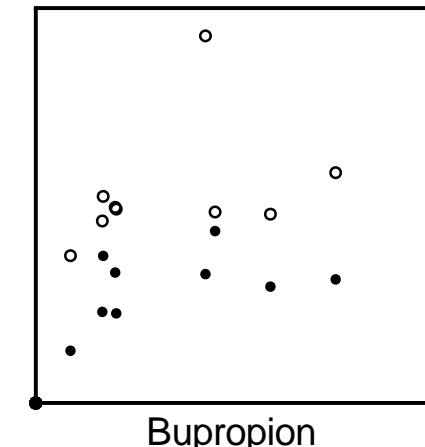
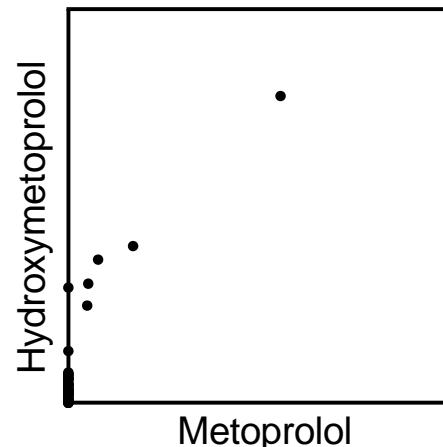
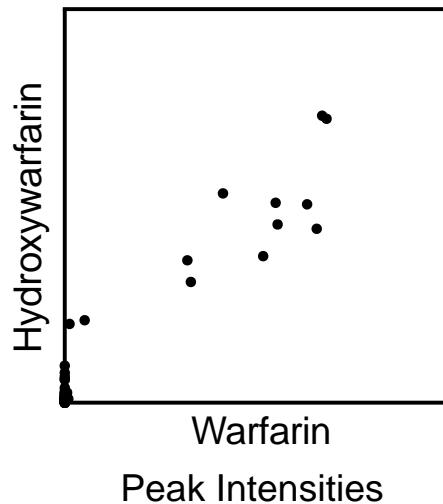
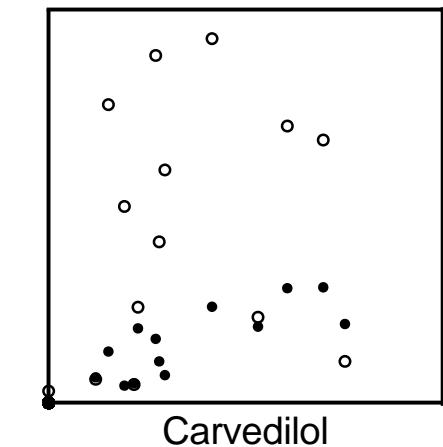
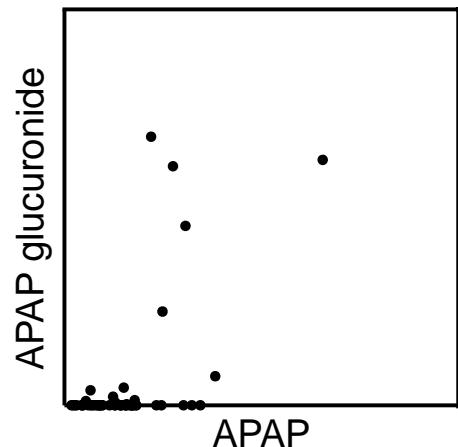
Hydroxycarvedilol (423.1911)**Hydroxycarvedilol O-Glucuronide (599.2231)****Supplementary Fig. 3.**

a) Correlation-based networks of parent xenobiotics shows parent xenobiotics are correlated with expected metabolites, source fragments, adducts, and isotopes in human plasma

b) Co-detection of related xenobiotics in human plasma samples with documented pharmaceutical use

S3b

- Hydroxycarvedilol
- Hydroxycarvedilol O-glucuronide



Peak Intensities

APAP glucuronide

APAP

Carvedilol

Hydroxywarfarin

Warfarin

Hydroxymetoprolol

Metoprolol

Bupropion

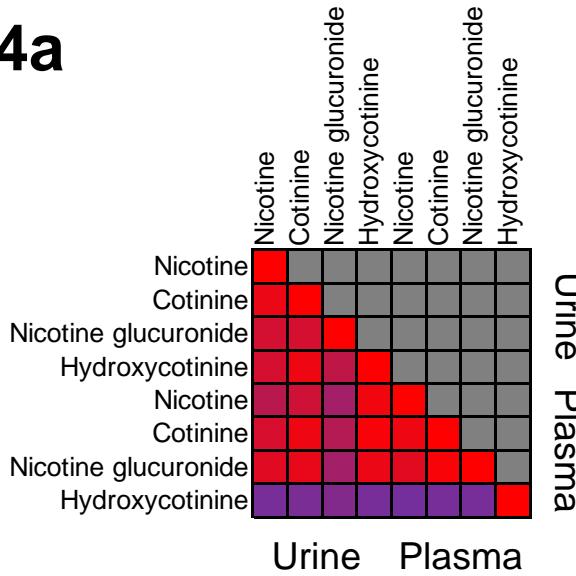
Peak Intensities

Supplementary Fig. 4.

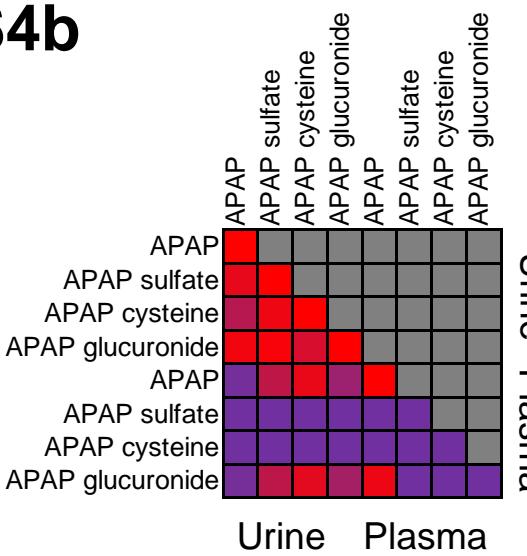
Correlation heat maps (Pearson's R) for xenobiotic and related biotransformation products across plasma and urine samples:

- a. Nicotine, b. Acetaminophen, c. Ibuprofen,
- d. Omeprazole, e. Naphthalene, f. Piperine

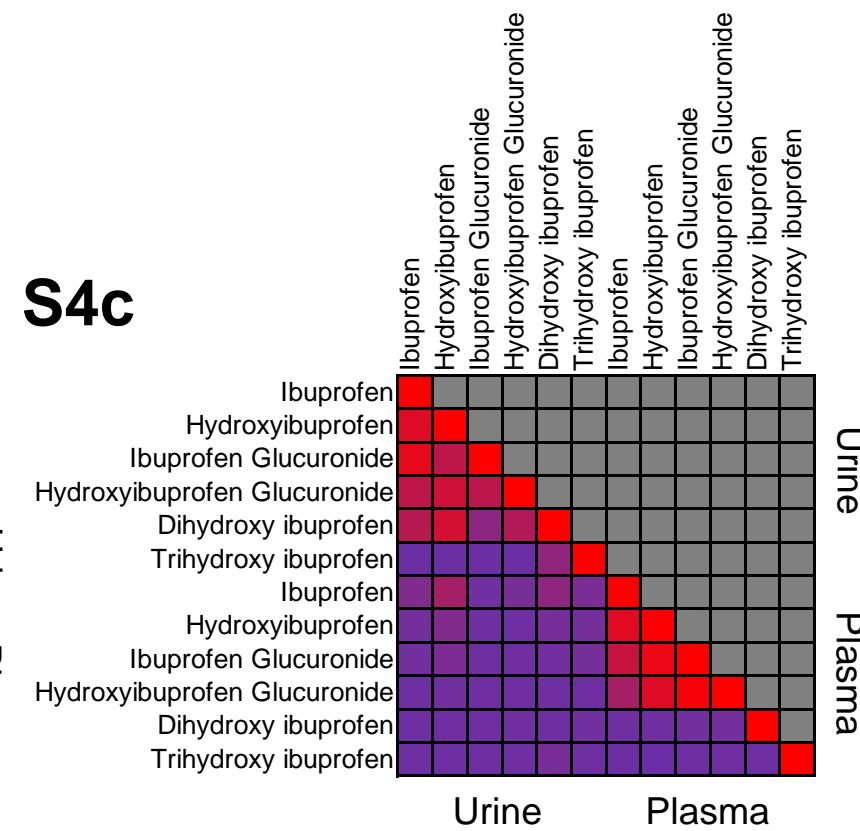
S4a



S4b

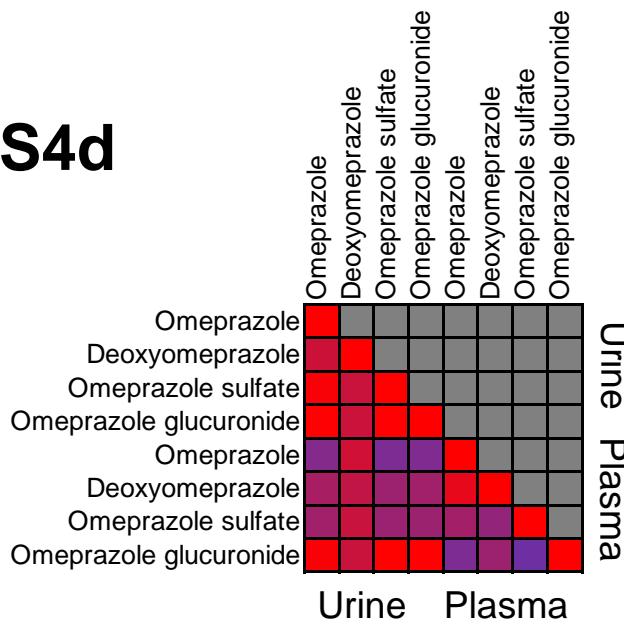


S4c

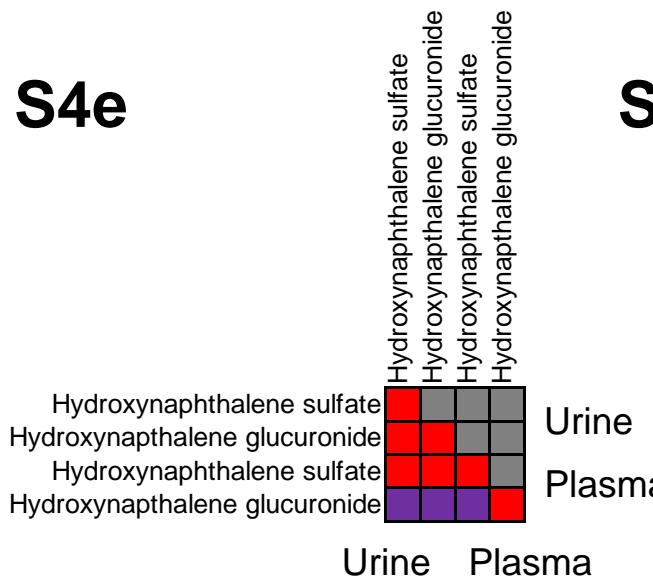


Pearson's R
-1 1

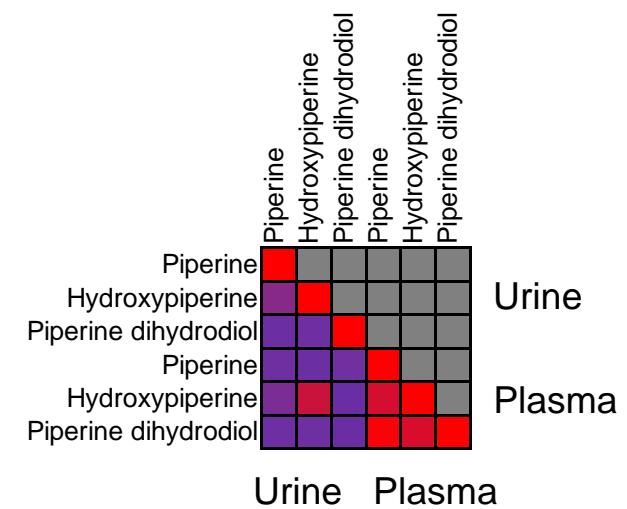
S4d

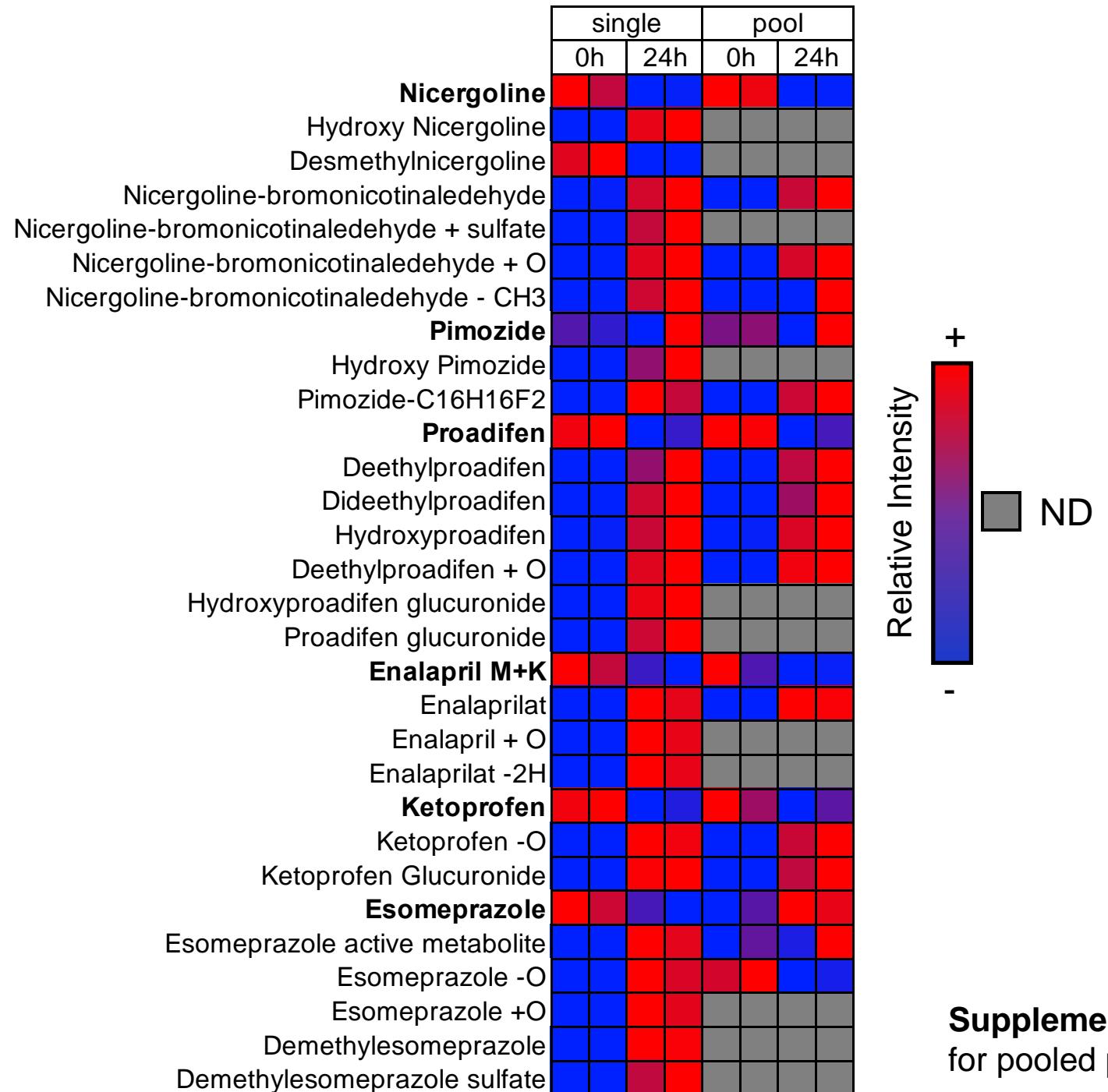


S4e



S4f





Supplementary Fig. 5. Comparison of S9 system performance for pooled precursors vs. single precursor incubations